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09/333,703	06/16/1999	PENG CHO TANG	243/245	4404

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EXAMINER
SPIEGLER, ALEXANDER H

ART UNIT	PAPER NUMBER
1637	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/333,703	Applicant(s) TANG ET AL.	
	Examiner SPIEGLER	Art Unit 1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *Amendment B filed 06/27/02* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Sharon N. Thornton
SHARON N. THORNTON
PATENT ANALYST

DETAILED ACTION

1. Claims 1-15 are pending. Claims 1-7 have been withdrawn from consideration as being drawn to non-elected subject matter. This action contains new rejections, which were not necessitated by Applicant's amendments, and therefore, this action is NON-FINAL.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 8-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 8-13 are indefinite over the recitation of "Formula I" because it is not clear as to what Formula I encompasses. Applicants could amend the claims to recite the actual formula of Formula I.

B) Claims 8-11 are indefinite over "one or more indolinone compounds" in step (a) of claim 8, because it is not clear as to whether said "one or more indolinone compounds" includes Formula I or not. If it does not, it is not clear as to how indolinone compounds of Formula I can be identified to inhibit growth factor stimulated cell proliferation. Applicants could amend the claims to recite, "one or more indolinone compounds of Formula I".

C) Claims 8-13 are indefinite because it is not clear as to what "effect" is being monitored.

D) Claims 12-13 are indefinite over "general disease symptoms" because it is not clear what is meant by this recitation. The specification, at best, teaches *possible* disease symptoms, such as ear nodulation, tail nodulation, nose swelling, paw swelling, and ballanitis. These possible symptoms do not provide a clear definition of what is encompassed by the term "general disease symptoms".

E) Claims 12-13 are indefinite over the recitation of "active" because it is not clear as to what it means when compounds are "active" in an adjuvant arthritis model. It is not as to whether these compounds "actively" treat arthritis in rats.

F) Claim 14 is indefinite over "modulating the activity of ... or modulating tyrosine kinase signal transduction" because it is not clear as to whether this is a method of modulating the activity of VEGF, FGF, or PDGF on cells in vivo or in vitro, *or* in modulating tyrosine kinase signal transduction. It is suggested that Applicants amend the claim to recite independent claims when claiming distinct methods with different goals.

G) Claim 14 is indefinite over "*in vitro*" because it is not clear as to how this method is a method "*in vitro*" when the first step comprises, "administering to a patient in need", which is a method *in vivo*.

H) Claims 14-15 are indefinite "said one or more compounds of formula I" because this recitation lacks antecedent basis.

I) Claim 14 is indefinite over "*one more* pharmaceutically acceptable recipients" because the claim does not refer to a first pharmaceutically acceptable recipient, only a "pharmaceutically acceptable composition".

J) Claims 14-15 are indefinite because it is not clear as to whether "and a five-membered ring" should be considered "open" or "closed" claim language. Applicants could amend the claims by deleting "and a five-membered ring heteroaryl ring, wherein said ring is selected from the group consisting of", thus, making one definite Markush group.

K) Claim 15 is indefinite over "solid tumor growth and metastases" because it is not clear as to what is encompassed by this recitation.

L) Claim 15 is indefinite over "excessive scarring during wound healing" because it is not clear as to what is meant by this recitation, and specifically, what is considered "excessive scarring".

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 14 and 15 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

With respect to claim 14:

Claim 14 is broadly drawn to a method of modulating abnormal cell proliferation, modulating the activity of VEGF, FGF or PDGF on cells in vivo or vitro or modulating tyrosine kinase signal transduction, comprising administering to a patient a pharmaceutically acceptable composition comprising a therapeutically effective amount of one or more compounds of

Formula I. Applicants have not adequate described these broad inventions in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The specification adequately describes the effects of Compounds II-IV of Formula I in assays of inhibiting *specific* growth factor stimulated cell proliferation (e.g. VEGF, PDGF, and FGF) in *specific* cells types (e.g. human vein endothelial cells and rat smooth muscle cells) (see Examples 2, 3 and 5). However, these specific examples do not adequately support the instant claims.

Methods of modulating abnormal cell proliferation, modulating the activity of VEGF, FGF or PDGF on cells in vivo or vitro, or modulating tyrosine kinase signal transduction encompasses an extremely vast genus of possible genes that could be activated or deactivated, as well as, possible proteins that have an altered expression, that the specification has not evaluated, let alone contemplated. For example, methods of modulating abnormal cell proliferation would encompass methods of evaluating the effects of compounds II-IV of formula I, in patients who are suffering of cancer or some other disease that results or is effected by the proliferation of cells. This alone would constitute a large genus of possible conditions, not described in the specification.

Therefore, the mere teaching of the effects of Compounds II-IV of Formula I in assays of inhibiting *specific* growth factor stimulated cell proliferation, in *specific* cells types does not adequately describe the broadly claimed genus. Applicants were not in possession of the claimed genus.

With respect to claim 15:

Claim 15 is drawn to a method of treating or preventing an abnormal condition by administering one or more compounds of Formula 1, wherein said abnormal condition is selected from the group consisting of arthritis, endometriosis, ocular neovascularization, solid tumor growth and metastases, and excessive scarring during wound healing.

The specification teaches the effects of Compounds II-IV of Formula I in an isolated animal model for a specific condition (i.e. adjuvant arthritis in a rat model) (Example 4). This single example does not provide an adequate written description of the claimed genus of abnormal conditions. For example, conditions comprising solid tumor growth and metastases comprises a large number of possible tumor types and metastases, in a wide range of possible cancers, none of which is described in the specification to reasonably convey to one of ordinary skill in the art that the inventors were in possession of this broadly claimed genus. Thus, there is not an adequate written description of the claimed genus.

6. Claims 14 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of inhibiting VEGF and FGF stimulated cell proliferation in human vein endothelial cells and inhibiting PDGF stimulated cell proliferation in smooth muscle cells by administering one or more compounds of Formula I, does not reasonably provide enablement for a method of modulating abnormal cell proliferation, modulating the activity of VEGF, FGF or PDGF on cells in vivo or vitro or modulating tyrosine kinase signal transduction, comprising administering to a patient a pharmaceutically acceptable composition comprising a therapeutically effective amount of one or more compounds of Formula I. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

In Ex parte Forman, 230 USPQ 546 (Bd. App. 1986), the Board considered the issue of enablement in molecular biology. In considering these factors: (a) in order to practice the invention, the practitioner must test the effects of one or more compounds of Formula I on a large number of possible cells and signaling pathways; (b) the specification provides guidance and working examples for evaluating the effects of Compounds II-IV of Formula I in assays of inhibiting *specific* growth factor stimulated cell proliferation (e.g. VEGF, PDGF, and FGF) in *specific* cells types (e.g. human vein endothelial cells and rat smooth muscle cells) (see Examples 2, 3 and 5); (c) the invention is directed to methods of modulating abnormal cell proliferation, modulating the activity of VEGF, FGF or PDGF on cells in vivo or vitro or modulating tyrosine kinase signal transduction, comprising administering to a patient a pharmaceutically acceptable composition comprising a therapeutically effective amount of one or more compounds of Formula I; (d) the prior art does not teach the effects on one or more compounds of formula I in methods of modulating abnormal cell proliferation, modulating the activity of VEGF, FGF or PDGF on cells in vivo or vitro or modulating tyrosine kinase signal transduction; (e) the level of skill in molecular biology is high; (f) the results of experiments involving modulating abnormal cell proliferation, modulating the activity of VEGF, FGF or PDGF on cells in vivo or vitro or modulating tyrosine kinase signal transduction with any possible compound of Formula I are not predictable; (g) the claims are broadly drawn, reciting any possible cells or signaling pathways.

Due to the large quantity of experimentation necessary to test any possible compound of Formula I for modulating abnormal cell proliferation, modulating the activity of VEGF, FGF or PDGF on cells in vivo or vitro or modulating tyrosine kinase signal transduction, the lack of direction/guidance presented in the specification regarding these broadly claimed methods, the

absence of working examples directed to compounds of Formula I that accomplish the claimed methods, the complex nature of the invention, the unpredictability of the effects of compounds of Formula I on the modulation of abnormal cell proliferation, for example, and the breadth of the claims, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

7. Claim 15 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating arthritis in a patient by administering one or more compounds of Formula I, does not reasonably provide enablement for treating or preventing endometriosis, ocular neovascularization, solid tumor growth and metastases, and excessive scarring during wound healing. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

In Ex parte Forman, 230 USPQ 546 (Bd. App. 1986), the Board considered the issue of enablement in molecular biology. In considering these factors: (a) in order to practice the invention, the practitioner must test the effects of one or more compounds of Formula I in patients suffering from endometriosis, ocular neovascularization, solid tumor growth and metastases, and excessive scarring during wound healing (which are distinct conditions requiring unrelated assays); (b) the specification provides guidance for treating a patient with arthritis with compounds II-IV of Formula I; (c) working examples are presented which only teach the treatment of compounds II-IV in a rat adjuvant arthritis model; (d) the invention is directed to methods of treating or *preventing* endometriosis, ocular neovascularization, solid tumor growth

and metastases, and excessive scarring during wound healing; (e) the prior art does not teach methods of treating or preventing with one or more compounds of Formula I or that the results of an rat adjuvant arthritis model can be extrapolated to enable methods of treating or preventing endometriosis, ocular neovascularization, solid tumor growth and metastases, and excessive scarring during wound healing; (f) the level of skill in molecular biology is high; (g) the results of experiments involving treating and preventing endometriosis, ocular neovascularization, solid tumor growth and metastases, and excessive scarring during wound healing is not predictable; (h) the claims are broadly drawn, reciting the treatment and prevention of unrelated conditions, such as endometriosis, ocular neovascularization, solid tumor growth and metastases, and excessive scarring during wound healing.

Due to the large quantity of experimentation necessary to treat and prevent endometriosis, ocular neovascularization, solid tumor growth and metastases, and excessive scarring during wound healing, the lack of direction/guidance presented in the specification regarding above treatment and prevention, the absence of working examples directed to the treatment and prevention of endometriosis, ocular neovascularization, solid tumor growth and metastases, and excessive scarring during wound healing, the complex nature of the invention, the unpredictability of the treatment and prevention of endometriosis, ocular neovascularization, solid tumor growth and metastases, and excessive scarring during wound healing, and the breadth of the claims, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Double Patenting

8. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible

harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

9. Claims 14 and 15 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 15-21 of U.S. Patent No. 5,792,783.

The instant claims embrace a substantial number of overlapping species of the '783 patent, and as such, embody a single inventive concept and thus, one invention.

Instantly claimed 14 is drawn to a method of modulating abnormal cell proliferation, modulating the activity of VEGF, FGF, or PDGF on cells in vivo or in vitro or **modulating tyrosine kinase signal transduction**, comprising administering a therapeutically effective amount of one or more compounds of Formula I. Instantly, claimed 15 is drawn to a method of **treating or preventing an abnormal condition** by administering a therapeutically effective amount of one or more compounds of Formula I, wherein said abnormal condition is selected from the group consisting of **arthritis**, endometriosis, and excessive scarring during wound healing.

The instantly claimed compound recites, "A is selected from the group consisting of a 4,5,6,7-tetrahydroindole and a five membered heteroaryl ring...". Thus, A can be a 4,5,6,7-tetrahydroindole **or** a five membered heteroaryl ring.

Tang et al. (USPN 5,792,783) teaches the use of the compounds of Formula I, wherein A is a five membered heteroaryl ring.

Specifically, Tang teaches:

"15. A method for **treating diseases related to tyrosine kinase signal transduction**, the method comprising the step of administering to a subject in need thereof a therapeutically effective amount of a compound of Formula I.

16. The method of claim 15 wherein said disease is selected from the group consisting of cancer, blood vessel proliferative disorders, fibrotic disorders, mesangial cell proliferative disorders and metabolic diseases.

17. The method of claim 16 wherein the blood vessel proliferative disorder is selected from the group consisting of **arthritis** and restenosis.

18. The method of claim 16 wherein the fibrotic disorder is selected from the group consisting of hepatic cirrhosis and atherosclerosis.

19. The method of claim 16 wherein the mesangial cell proliferative disorder is selected from the group consisting of glomerulonephritis, diabetic nephropathy, malignant nephrosclerosis, thrombotic microangiopathy syndromes, transplant rejection and glomerulopathies.

20. The method of claim 16 wherein the metabolic disorder is selected from the group consisting of psoriasis, diabetes melitus wound healing, inflammation and neurogenerative diseases.

21. **A method for regulating, modulating or inhibiting tyrosine kinase signal transduction** comprising administering to a subject a therapeutically effective amount of a compound of Formula I." (col. 64, ln. 16 to col. 65, ln. 52).

Conclusion

10. No claims are allowable.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alexander H. Spiegler whose telephone number is (703) 305-0806. The examiner can normally be reached on Monday through Friday, 7:00 AM to 3:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's

supervisor, Gary Benzion can be reached on (703) 308-1119. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 and (703) 305-3014. Applicant is also invited to contact the TC 1600 Customer Service Hotline at (703) 308-0198.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Alexander H. Spiegler
September 30, 2002

KENNETH R. HORLICK, PH.D
PRIMARY EXAMINER

9/30/02